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The Role of Double Dissociation Studies in the Search for Candidate Endophenotypes for the Comorbidity of Attention Deficit Hyperactivity Disorder and Reading Disability

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The neuropsychological underpinnings of Attention Deficit Hyperactivity Disorder (ADHD) and Reading Disability (RD) and their comorbidity may be studied usefully with the double dissociation design. The results of studies using the double dissociation method may be linked to the search for an endophenotype of ADHD and RD and their comorbidity. This endophenotype may eventually shed more light on the genetic origins of both ADHD and RD and their comorbidity. Executive functioning appears to be a candidate endophenotype of the comorbidity of ADHD and RD. Future studies, it is argued, should combine both the double dissociation design with the Additive Factor Method in this endeavour. Additionally, more attention needs to be given to the subtypes of ADHD, RD, and their association with Dyscalculia to determine useful endophenotype(s).

Keywords: *Attention Deficit Hyperactivity Disorder; Comorbidity, Double dissociation; Endophenotype; Reading Disability; Subtype*

Introduction

Attention Deficit Hyperactivity Disorder (ADHD) and Reading Disability (RD) occur together more often than would be expected by chance. Genetic molecular studies show that the comorbidity of ADHD and RD may have genetic origins

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(Stevenson et al., 2005). However, the results of these studies are not always clear and are sometimes contradictory. A reason for these unclear and contradictory findings could be that ADHD and RD are heterogeneous disorders—a fact that is not taken into account in these genetic studies. Identification of endophenotypes could assist in the search for the genetic base of the comorbidity of ADHD and RD. An endophenotype could be a neuropsychological marker of a disorder and is a closer expression of the genotype of the disorder than is the phenotype. It is possible that subtypes of ADHD and RD have different endophenotypes. If this is so, then it is also possible they have different genotypes, which would explain the unclear results of the genetic molecular studies. Given this and the recent interest in determining the endophenotype of ADHD (Doyle et al., 2005), it is a challenge to the field to discover those neuropsychological deficits that are distinctive to the two disorders and those that are common.

This article will discuss neuropsychological studies that test three behavioural genetic hypotheses about the comorbidity of ADHD and RD. The neuropsychological studies that test the three hypotheses all use a double dissociation design. This article also attempts to provide a brief rationale for a research agenda in the area by indicating the advantages of combining the strengths of the double dissociation design with the Additive Factor Method (AFM) in studies of ADHD and RD and their comorbidity, as well as their association with Dyscalculia.

We begin with a brief account of the comorbidity of ADHD and RD, followed by a description of the single and double dissociation methods. This is followed by a section on current findings of studies using these methods that place this approach in the context of the three behavioural genetic hypotheses of the two disorders.

ADHD, RD, Comorbidity, and Endophenotypes

ADHD occurs in approximately 5% of school-aged children (American Psychiatric Association, 1994) and frequently occurs with other psychiatric and developmental disorders (Angold, Costello, & Erkanli, 1999). For example, ADHD is often associated with Learning Disabilities (LD) such as Reading Disability (RD) (Faraone et al., 1993). Earlier estimates of the comorbidity of RD and ADHD varied widely (9–80%) (August & Garfinkel, 1989; Halperin, Gittelman, Kline, & Rudel, 1984; Holborow & Berry, 1986; Lambert & Sandoval, 1980); however, more recent research estimates the comorbidity of ADHD and RD to be 40% (Shaywitz, Escobar, Shaywitz, Fletcher, & Makuch, 1992).

Twin studies indicate that both disorders (ADHD and RD) have genetic origins (Hudziak et al., 1998; Pennington et al., 1991; Rhee, Waldman, Hay, & Levy, 1999; Sherman, Iacono, & McGue, 1997). However, the exact locations of the possible genes that may lead to ADHD and/or RD are currently unknown (Faraone et al., 2005; Rabin, Wen, Hepburn, Lubs, & Feldman, 1993). Some evidence suggests that ADHD and RD co-occur because of shared genetic factors (Gilger, Pennington, & DeFries, 1992). However, twin studies and molecular genetic studies of RD and

ADHD often have low statistical power to detect genes of small effect, possibly because of the heterogeneity of both disorders (Faraone, Tsuang, & Tsuang, 1999).

Recent conceptualisations of the underpinnings of mental disorders suggest a search be undertaken for the endophenotypes of ADHD and RD (Almasy & Blangero, 2001; Doyle et al., 2005; Gottesman & Gould, 2003). An endophenotype may be a biochemical, neurophysiological, endocrinological, neuroanatomical, cognitive, or neuropsychological marker(s) of a disorder. To be a candidate endophenotype, markers should be heritable. An endophenotype is genetically less complex, has a more direct biological link to the disorder, and is supposed to be influenced by one or more of the susceptible genes of the disorder. In this article, we propose to advance the search for the endophenotypes of ADHD and RD by establishing that neuropsychological studies with this purpose should be conducted using a double dissociation design.

Neuropsychology and Searching for Endophenotypes

As will become evident from this brief selective review of neuropsychological studies of both disorders, deficits associated with ADHD and RD show communality more often than distinctiveness between the disorders (Sergeant, Geurts, & Oosterlaan, 2002). This is somewhat surprising given that the two disorders are hypothesised to be associated with distinct brain mechanisms. For example, ADHD is suggested to be a disorder of frontal lobe functioning (Barkley, 1997), the right anterior cingulate gyrus (Bush et al., 1999) and the cerebellum (Castellanos & Tannock, 2002). In contrast, magnetic resonance imaging studies have shown RD to be associated with the planum temporale (Foster, Hynd, Morgan, & Hugdahl, 2002; Hynd, Semrud-Clikeman, Lorys, Novey, & Eliopulos, 1990). More recently, it has been shown that leftward asymmetry in the temporal bank of the planum temporale is related to better coding and storage of semantic material (Kibby et al., 2004). Kibby et al. noted that the parietal bank morphology is related to coding and storage of phonological material, and that the presence of an extra gyrus in the parietal region is associated with reduced phonological working memory. Thus, at first glance one would expect that children with ADHD and children with RD would exhibit distinctive patterns of neuropsychological dysfunction. However, recent neural imaging research indicates that phonological processing in working memory, apart from requiring dorsolateral prefrontal functioning, is also dependent upon cerebellar functioning (Desmond, Gabrieli, Wagner, Ginier, & Glover, 1997). Hence, both ADHD and RD may have communalities in working memory but dissociations in other brain networks.

In order to disentangle those functional deficits that co-occur and those that occur separately in ADHD and RD, we propose that a double dissociation design be employed. A double dissociation between these two disorders would be supported if ADHD and RD exhibit distinctive profiles on two contrasting neuropsychological domains (Pennington, Groisser, & Welsh, 1993; Willcutt, Pennington, Olson, Chhabildas, & Hulslander, 2005). The results of this type of research have implications for our understanding of the neuropsychological mechanisms of

ADHD and RD and their comorbidity, as well as for our search for endophenotypes. If the two disorders could be separated on the two contrasting neuropsychological functions or cognitive domains, this would be evidence that ADHD and RD have distinct aetiologies. If on the other hand, a double dissociation did not occur between ADHD and RD, it could be concluded that ADHD and RD have a common aetiology.

To test for a double dissociation of the two disorders, we first need to be able to identify the neuropsychological deficits of ADHD and RD separately. Research indicates that ADHD may be characterised by several neuropsychological dysfunctions. An example of a neuropsychological dysfunction of ADHD is a deficit in executive functioning, particularly in inhibition and working memory (Pennington & Ozonoff, 1996). Other neuropsychological dysfunctions of ADHD indicate working memory and cerebella deficits, such as difficulties in time perception (Tiffin-Richards, Hasselhorn, Richards, Banaschewski & Rothenberger, 2004) and deviant sensitivity to reward and punishment (Luman, Oosterlaan, & Sergeant, 2005). RD, on the other hand, may be characterised by phonological deficits and naming deficits (Wagner & Torgesen, 1987; Wolf & Bowers, 2000).

There is some evidence from twin research and family research that executive functioning, and working memory in particular, are heritable, which makes executive functioning deficits candidates for the endophenotype of ADHD (Ando, Ono, & Wright, 1995; Fan, Wu, Fosella, & Posner, 2001). Phonological skills are also influenced by genetic factors, and deficits in phonological skills may be a possible candidate endophenotype of RD (Castles, Datta, Gayan, & Olson, 1999). Here, we review double dissociation studies in which executive functions and the executive function of working memory—in particular, timing, naming, and phonological skills—have been studied in ADHD and RD. These double dissociation studies examine the neuropsychological underpinnings of the comorbidity of ADHD and RD, and are a first phase in determining the endophenotype.

First, we will describe the double dissociation methodology used in the studies that are discussed in this article. Second, studies using a single dissociation design, which are the basis for double dissociation studies, will be noted. Double dissociation studies can be used to investigate whether neuropsychological variables that have been identified as associated with ADHD and RD in single dissociation studies show overlap on distinctiveness with respect to the two disorders. Third, the double dissociation methodology will be linked to three behavioural genetic hypotheses related to the comorbidity of RD and ADHD. Finally, the results of the behavioural genetic studies will be reviewed to suggest ways in which double dissociation research in ADHD and RD can be improved and thus increase the likelihood of uncovering the endophenotype of the two disorders.

Single and Double Dissociation Methodology and the AFM

In this section we define the methodological terms, and then identify the principles that we hope will be applied in discovering the endophenotypes of ADHD and RD.

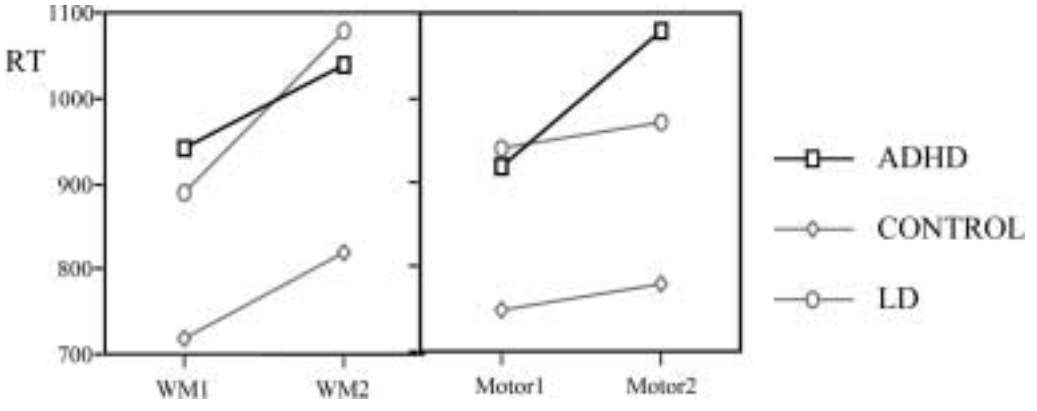

Figure 1. The double dissociation methodology in combination with the AFM used in van der Meere et al.'s (1989) study of children with ADHD, children with LD, and controls with two tasks (a working memory task and a motor task) at two levels of difficulty. The *y* axis represents reaction times, with slower times indicating greater difficulty with the task.

We will illustrate this using previous research conducted by one of the authors and other colleagues with children with LD and children with ADHD (van der Meere, van Baal, & Sergeant, 1989) and use a figure based on the data from that publication for this purpose.

Single dissociation studies compare two or more groups with one another using a single task as the dependent measure. The double dissociation method, on the other hand, requires two tasks to be employed (e.g., the tasks depicted in the left and right panels of Figure 1) to determine whether one of the two tasks, here a working memory task, shows an interaction with one clinical group (here the LD group), but not the other clinical group (the ADHD group). This would be expressed as a statistically significant interaction between groups with task. The findings in Figure 1 suggest that a working memory deficit is specific to LD and a motor selection deficit is specific to ADHD.

The double task methodology has been applied in previous studies of ADHD and RD, but these studies have used only a single level of task difficulty (see later). As Figure 1 makes clear, at the level of difficulty of WMI and Motor 1, there is no difference between the ADHD and RD groups, and both groups are different from the control group. In contrast, if only tasks at the difficulty level of WM2 and Motor 2 had been used, all three groups would be distinguishable. The results of using experimental tasks with a single level of difficulty clearly fail to present a complete picture, and the evidence represented in Figure 1 indicates the need to include tasks with more than one level of difficulty in double dissociation research.

Use of multi-task difficulty levels is a sine qua non of the AFM (Sternberg, 1969). The clinical application of the AFM states that if a task variable with increasing task demands separates a clinical group from the control or other clinical group, then the neuropsychological process operationalised by the task variable is defective

(Sergeant, 2005; Sergeant, Oosterlaan, & van der Meere, 1999; Sergeant & van der Meere, 1990). This process is identified by the interaction between group and task. If the reader examines Figure 1, three types of differences between the clinical and control groups can be observed. First, in both panels the clinical groups are significantly different from the controls. Second, there is an interaction (slope difference) between groups and task level: clinical groups do less well with increasing task demands than the controls. Third, there is a three-way interaction of group with task level and type of task. If only one level of task had been used, the specific process deficit would not have been revealed because there would have been no task slope effect present. It is the combination of double task methodology and AFM that we propose is essential for the discovery of the endophenotypes of ADHD and RD.

Single Dissociation Studies with ADHD and RD

Before discussing studies using the double dissociation design, reports using the single dissociation design will be reviewed briefly. These studies use a single task in order to examine whether individuals with ADHD and RD differ in their performance. Single dissociation studies can potentially aid in the search for suitable neuropsychological processes that might differentiate ADHD and RD in the double dissociation design.

ADHD is often associated with deficits in executive functioning (for a review see Sergeant et al., 2002). Executive functions include planning, evaluation, inhibition and changing one's actions. Additional executive functions are working memory and fluency. Although children with ADHD have difficulties in all these areas of executive functioning, they especially exhibit deficits in inhibition and working memory (Barkley, 1997). While executive functioning deficits have been found in children with ADHD (Pennington & Ozonoff, 1996; Sergeant, Geurts, Huijbregts, Scheres, & Oosterlaan, 2003), it is unclear, however, whether the comorbidity of LD such as RD and Dyscalculia with ADHD has an effect on the executive functions of children with either ADHD or LD, because executive functioning deficits may also occur in children with only RD (Donfranesco, Mugnaini & Dell'Uomo, 2005). Seidman, Biederman, Monuteaux, Doyle, and Faraone (2001) examined the executive functions of children with ADHD, with and without LD, in comparison with control children. They demonstrated that children with both ADHD and LD had more difficulty with executive functioning compared with children with only ADHD and control children. When children with ADHD had both Dyscalculia and RD, they were more impaired than children with ADHD with a single LD. A comorbid learning disability thus appears to aggravate the executive functioning deficits of children with ADHD.

Working memory deficits have also been shown in children with ADHD (see Martinussen, Hayden, Hogg-Johnson, & Tannock, 2005, for a meta-analysis). However, working memory deficits have also been reported in RD (Chiappe, Hasher, & Siegel, 2000; De Jong, 1998). Douglas and Benezra (1990) studied the nature of verbal short-term and long-term memory in boys with ADHD and in boys with RD.

Boys with ADHD demonstrated both long-term and short-term memory difficulties. However, they were the most impaired on memory measures that required self-regulatory processes or "executive" processing; that is, children with ADHD had more difficulty organising, using rehearsal strategies, sustaining strategic effort, and considering response alternatives. In contrast, boys with RD had more difficulty with memory tasks that demanded verbal processing. A study by Kaplan, Dewey, Crawford, and Fisher (1998) demonstrated that the long-term memory difficulties of children with ADHD may be due to inattentiveness rather than reflecting specific memory deficits. Kaplan et al. studied long-term memory in children with ADHD, children with RD, and children with both ADHD and RD in order to separate the influence of inattentiveness from memory. The findings demonstrated that children with RD and children with both ADHD and RD had difficulties in recalling information. However, children with only ADHD did not have difficulty in remembering; they were impaired on memory tasks that required attention.

Another important process for the identification of the ADHD endophenotype is timing. Children with ADHD demonstrate time perception deficits (van Meel, Oosterlaan, Heslenfeld, & Sergeant, 2005; Rubia, Taylor, Taylor, & Sergeant, 1999; Smith, Taylor, Warner Rogers, Newman, & Rubia, 2002). The role of comorbid RD in studies with ADHD that examine time perception deficits is, however, unclear. Tiffin-Richards et al. (2004) studied time reproduction in finger-tapping tasks in children with ADHD, children with RD, children with both ADHD and RD, and non-diagnosed controls. The clinical groups did not differ from controls on the time reproduction tasks. However, children with RD and children with both RD and ADHD were more impaired in tapping complex rhythms than the ADHD group. Toplak, Rucklidge, Hetherington, John, and Tannock (2003), in contrast, demonstrated deficits in duration discrimination and duration estimation in children and adolescents with ADHD with and without comorbid RD. However, the temporal information processing issue in ADHD is complex and awaits definitive research (Toplak, Dockstader, & Tannock, 2006).

An important process in identifying a RD endophenotype is establishing automatisation difficulties, which can be observed in tasks that require rapid naming of stimuli (Denckla, 1972). Children with ADHD also appear to have difficulties in rapid naming of stimuli (Tannock, Martinussen, & Frijters, 2000). Raberger and Wimmer (2002) studied rapid naming and balance in children with ADHD, children with both ADHD and RD, children with only RD, and controls. Both rapid naming and balance are thought to be mediated by the cerebellum (Raberger & Wimmer, 2002). In that study, children with RD with or without ADHD were most impaired at letter and colour naming. Children with ADHD either with or without RD had poor balancing skills in comparison with the other groups.

Another process important for RD is phonological processing (Lyon, 1995). Breier, Gray, Fletcher, Foorman, and Klaas (2002) studied temporal order judgement and discrimination in children with RD, children with ADHD, children with both ADHD and RD, and non-diagnosed controls. Children with RD demonstrated a specific deficit in speech perception compared with the ADHD groups,

while the ADHD and RD groups did not differ in processing non-speech stimuli. Consequently, Breier et al. suggested that children with RD have a deficit in phoneme perception.

Various single dissociation studies examining executive functions, memory, time perception, naming, and phonological skills in children with ADHD or RD or with ADHD and RD have been reported. These neuropsychological functions seem to be present in both disorders with the exception of phonological processing. However, differences or failure to distinguish between ADHD and RD groups in single dissociation studies are difficult to interpret. Although group effects may occur, they do not implicate a processing deficit. Failures to observe a group difference may occur due to floor effects. Hence, in order to implicate processing deficiencies, procedures are required that manipulate the processing demands of the task.

In the next section, the neuropsychological variables noted earlier will be explored in double dissociation studies of ADHD and RD in the context of studies involving the behavioural genetic hypotheses of the two disorders. Studies with a double dissociation design may provide greater specificity of dysfunction in both ADHD and RD.

Double Dissociation and Genetic Hypotheses

In the following section we illustrate how the double dissociation design may be used to test three behavioural genetic hypotheses concerning the comorbidity of ADHD and RD.

The three relevant hypotheses are the phenocopy hypothesis, the common aetiology hypothesis, and the cognitive subtype hypothesis, and these will be described in the following. A fourth hypothesis, the cross-assortment hypothesis, will not be discussed since it does not provide clear predictions for the double dissociation design (Faraone et al., 1993).

Phenocopy Hypothesis

The phenocopy hypothesis proposes that one disorder may lead to a copy of the symptoms of the other disorder (Pennington et al., 1993). The phenocopy hypothesis is supported when a double dissociation is found between two pure clinical groups; for example, ADHD and RD and the comorbid group is characterised by the neuropsychological deficit of one of the two pure groups. Pennington et al. tested three groups of children—namely, children with ADHD, children with comorbid ADHD and RD, and children with RD—on a variety of tasks of executive function and phonological skill. They reported a double dissociation between ADHD and RD, while the children with only ADHD exhibited executive functioning problems and the children with RD exhibited difficulties in phonological functioning. The comorbid group generally reflected the neuropsychological profile of the RD group. Pennington et al. interpreted their results as indicating that in children with ADHD and RD the symptoms of ADHD might occur due to untreated RD, but they did not really have ADHD.

The results of Pennington et al. (1993) have been partially replicated by Närhi and Ahonen (1995). No double dissociation was observed; that is, children in all three groups, exhibited executive dysfunctions. The comorbid group exhibited naming problems, as did the RD group. The difference between the two studies may be due to the tasks used, task difficulty levels, or the severity of ADHD and RD.

Common Aetiology Hypothesis

The common aetiology hypothesis suggests that ADHD and RD have common genetic origins. This hypothesis is supported when similar deficits are found in all the three groups. One common underlying deficit is thought to lead to different disorders (Willcutt et al., 2005).

Evidence for the common aetiology hypothesis was provided by Willcutt et al. (2005), who found evidence that children with ADHD demonstrated deficits in response inhibition, and children with RD had deficits in reading performance. However, the RD group also demonstrated response inhibition deficits. This latter finding argues against a double dissociation between ADHD and RD. In addition, the comorbid group demonstrated deficits in response inhibition and reading. The children with ADHD, those with RD, and children with both ADHD and RD all exhibited difficulties in processing speed and verbal working memory. Since the three groups had overlapping deficits, Willcutt et al. concluded that RD and ADHD have a common genetic basis.

In order to establish whether ADHD and RD have a common or distinct aetiology, Roodenrys, Koloski, and Grainger (2001) investigated working memory mechanisms; namely, the phonological loop and the central executive in children with RD, and in children with both ADHD and RD. Control and attention regulation processes are said to take place in the central executive (Baddeley & Logie, 1999), which is required for the retrieval of information in long-term memory and is a modality-free component of working memory. The phonological loop stores and rehearses verbal information for a short period to prevent it from decaying (Baddeley & Logie, 1999). The children with RD exhibited greater difficulty on the phonological loop task than the control group, while the comorbid group performed less well than the control group on two tasks that involved both the phonological loop and the central executive. Unfortunately, children with only ADHD did not participate in this study. Thus, this study cannot directly demonstrate that central executive deficits are specific to ADHD. Nevertheless, extension and replication of these findings would be important for the field.

Cognitive Subtype Hypothesis

The cognitive subtype hypothesis suggests that children with both ADHD and RD have a different form or more severe form of ADHD or RD than children with either disorder alone (Rucklidge & Tannock, 2002). This hypothesis would be supported if a double dissociation is found between the groups with a single

disorder of ADHD and RD (Rucklidge & Tannock, 2002) and there is evidence that the comorbid group has greater neuropsychological deficits than groups with a single disorder.

Willcutt et al. (2001) did find evidence for this hypothesis, reporting a double dissociation between ADHD and RD; that is, the children with ADHD had difficulties in executive functioning (e.g., inhibition, vigilance, and set sifting). Children with RD exhibited phonological deficits and verbal working memory deficits. Children with both RD and ADHD were more impaired on inhibition and phonological measures than the group with only ADHD, only RD, and controls. These results suggest that ADHD and RD are two separate disorders. The children in the comorbid group had a more severe subtype of ADHD and RD than the children with only ADHD and only RD, which is consistent with and provides support for the cognitive subtype hypothesis.

Rucklidge and Tannock (2002) found additional evidence in support of the cognitive subtype hypothesis. A double dissociation was reported; specifically, naming and working memory deficits were characteristic of RD, and inhibition deficits were characteristic of ADHD. In contrast, the comorbid ADHD and RD group exhibited both inhibition deficits and working memory deficits. The comorbid group exhibited more severe naming problems in the letter and number conditions than the two single disorder groups. This finding indicates that the comorbid group had a more severe automatisation problem than the children with only ADHD or RD, suggesting that automatisation would be a good candidate for future endophenotypic studies into comorbid ADHD and RD.

McGee, Brodeur, Symons, Andrade, and Fahie (2004) also provided support for the cognitive subtype hypothesis. They studied time perception and auditory working memory in children with ADHD, children with comorbid ADHD and RD, and children with only RD. It was found that children with ADHD had difficulty estimating the duration of a task that they had previously performed. Children with RD had difficulty with an auditory working memory task. Children with both ADHD and RD had more difficulty estimating the duration of a task than the single disordered groups, suggesting the importance of time estimation in differentiating ADHD and RD.

To summarise this section, three behavioural genetic hypotheses concerning the comorbidity of ADHD and RD have been studied using the double dissociation method. Executive functions such as working memory, as well as functions such as timing, naming, and phonological skills, have been studied in ADHD and RD using the double dissociation design. Taken together, the results of these studies suggest that executive functioning deficits occur in children with ADHD and children with both ADHD and RD (Rucklidge & Tannock, 2002; Willcutt et al., 2001). Nevertheless, there are reports of executive functioning deficits that occur in children with RD only (Närhi & Ahonen, 1995; Willcutt et al., 2005). The role of timing and naming deficits is unclear in the comorbidity of ADHD and RD, and requires further study (McGee et al., 2004; Rucklidge & Tannock, 2002). Furthermore, phonological deficits do not seem to occur in those with ADHD only and thus

provide a potentially fruitful base for neuro-endophenotypic research (Pennington et al., 1993; Rucklidge & Tannock, 2002; Willcutt et al., 2001).

Discussion

In the search for a candidate endophenotype of the comorbidity of ADHD and RD, several studies have been discussed which test for a double dissociation between ADHD and RD. In the double dissociation studies mentioned earlier, overlap in executive functioning deficits, particularly in inhibition and working memory, has been shown in ADHD and RD (Roodenrys et al., 2001; Willcutt et al., 2005). In contrast, processes such as timing, rapid naming, and phonological skills appear to separate ADHD and RD (McGee et al., 2004; Rucklidge & Tannock, 2002; Willcutt et al., 2001).

The double dissociation studies tested three hypotheses regarding the underpinnings of ADHD and RD, all of which have been supported in research, even though these hypotheses are contradictory about the nature of the comorbidity of ADHD and RD. The results of the neuropsychological double dissociation studies mentioned earlier in combination with recent genetic studies suggest that the phenocopy hypothesis regarding the nature of the comorbidity of ADHD and RD has little support. Recent genetic molecular studies that have shown comorbid ADHD and RD is associated with contributions of the ADRA2A gene (Stevenson et al., 2005) might provide support for the cognitive subtype hypothesis. This gene seems to play an important role in working memory. It appeared in the double dissociation studies that working memory might be a good candidate endophenotype of the comorbidity of ADHD and RD, which seems to be validated by Stevenson et al. Other genetic research seems to support both the cognitive subtype hypothesis and the common aetiology hypothesis. Gayán et al. (2005), using bivariate linkage scans, found various genes that have an effect on both ADHD and RD. They found a new gene, 14q32, that could be implicated in the symptoms of both ADHD and RD. Other genes that previously seemed to be involved in the single disorders of ADHD and RD were suggested to have effects on both ADHD and RD. Other genes that are supposed to be associated with ADHD or RD could not show bivariate linkage.

The genetic studies could reflect the results of the behavioural genetic hypotheses tested with the double dissociation design. Genetic research has shown that both ADHD and RD are heterogeneous disorders. Probably, some subtypes of ADHD and RD have the same genetic origins, but other subtypes ADHD and RD are separate disorders. These genetic studies could assist to differentiate which subtypes of ADHD and RD show overlap on executive functioning deficits, and which subtypes of ADHD and RD differ regarding the involvement of executive functioning.

Subtyping of ADHD in future double dissociation studies with ADHD and RD is important because the subtypes of ADHD have different estimates of comorbidity with other disorders. ADHD-inattentive subtype (ADHD-IA), for example, seems to co-occur more often with LD and internalising disorders than with ADHD-Combined

(ADHD-C) (Willcutt & Pennington, 2000). Furthermore, the inattentive behaviour is associated more with RD than with hyperactivity (Weiler, Bernstein, Bellinger, & Waber, 2000; Willcutt & Pennington, 2000). However, the (neuropsychological) distinctiveness of ADHD-C and ADHD-IA appears unclear. Klorman et al. (1999) demonstrated that children with ADHD-C had more difficulty with planning and in cognitive flexibility than children with ADHD-IA. Nigg, Blaskey, Huang-Pollock, and Rappley (2002) reported children with the ADHD-C subtype exhibited more difficulties with response inhibition than children with ADHD-IA. In contrast, Geurts, Verté, Oosterlaan, Roeyers, and Sergeant (2005) reported that the ADHD-C and ADHD-IA subtypes could not be differentiated from one another on inhibition and working memory tasks, thus replicating earlier research (Barkley, Grodzinsky, & DuPaul, 1992; Chhabildas, Pennington, & Willcutt, 2001). A reason for the contradictory results might be that ADHD-IA could be subdivided into two subtypes, so far overlooked in neuropsychological studies. One type is characterised by a cognitive sluggish tempo that is reflected in inconsistent alertness, orientation, and daydreaming. The other ADHD-IA subtype may be distinguished by distraction problems (Geurts et al. 2005).

Subtypes of RD have also not been taken into account in double dissociation studies. Various subtypes may be distinguished in RD; that is, children with RD read either fast but inaccurately or read slowly but accurately (Bakker, 1979; Manis, Seidenberg, Doi, McBride-Chang, & Petersen, 1996). Inhibition has been found to be disturbed in a subtype of children with RD typified as being fast guessers (van der Schoot, Licht, Horsley, & Sergeant, 2000). It seems that some of the subtypes of RD show overlap with ADHD.

An additional point of concern in ADHD and RD endophenotypes is that there is an association with Dyscalculia in both disorders. Dyscalculia co-occurs frequently with RD and ADHD (Gross-Tsur, Manor & Shalev, 1996). These authors found that 26% of children with Dyscalculia also had ADHD. The incidence of Dyscalculia in ADHD was (in that study) five times higher than in the normal population. In 17% of the children with Dyscalculia, RD was also observed. Children with Dyscalculia exhibited higher rates of attentional problems than controls on the Child Behavior Checklist (Achenbach & Edelbrock, 1983; Shalev, Auerbach & Gross-Tsur, 1995). Dyscalculia may also be characterised by working memory deficits and attention difficulties similar to those of children with ADHD (Koontz & Berch, 1996; Lindsay, Tomazic, Levine, & Accordo, 1999; Siegel & Ryan, 1989).

As illustrated by Figure 1, future double dissociation studies should include tasks with two levels of difficulty to ensure that the process measured by the task can be determined and any differences between groups exposed. In the majority of studies mentioned here, tasks with one level were used. With this method only group main effects could be demonstrated (Chapman & Chapman, 1973). The AFM in combination with the double dissociation design could further unravel which subtypes of ADHD and RD overlap and which do not. When these endophenotypes are found, the search for the genetic origins of ADHD and RD and their comorbidity may be based on an understanding of the distinctive as well as overlapping functional deficits.

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